REVIEW

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Sepsis and septic shock: Guideline-based management

ABSTRACT

Sepsis is a life-threatening organ dysfunction that results from the body's response to infection. It requires prompt recognition, appropriate antibiotics, careful hemodynamic support, and control of the source of infection. With the trend in management moving away from protocolized care in favor of appropriate usual care, an understanding of sepsis physiology and best practice guidelines is critical.

KEY POINTS

Tools such as the Systemic Inflammatory Response Syndrome criteria and the quick version of the Sequential Organ Failure Assessment can help with early diagnosis and triage.

The initial antibiotic should be broad-spectrum, based on local sensitivity patterns, with daily assessment of appropriate antibiotic de-escalation and cessation.

Resuscitation with initial fluid boluses should be followed by weighing benefits and risks of additional fluid administration based on dynamically assessed volume status, and then aggressive fluid removal during recovery.

During resuscitation, a goal mean arterial pressure of 65 mm Hg is preferred, using norepinephrine (with vasopressin if needed) to achieve it.

Glucocorticoids are not recommended if fluid resuscitation and vasopressors are sufficient to restore hemodynamic stability.

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Sepsis and particularly septic shock should be recognized as medical emergencies in which time matters, as in stroke and acute myocardial infarction. Early recognition and rapid institution of resuscitative measures are critical. But recognizing sepsis can be a challenge, and best management practices continue to evolve.

This article reviews guidance on the diagnosis and management of sepsis and septic shock, with attention to maximizing adherence to best practice statements, and controversies in definitions, diagnostic criteria, and management.

COMMON AND LIFE-THREATENING

Sepsis affects 750,000 patients each year in the United States and is the leading cause of death in critically ill patients, killing more than 210,000 people every year.[1] About 15% of patients with sepsis go into septic shock, which accounts for about 10% of admissions to intensive care units (ICUs) and has a death rate of more than 50%.

The incidence of sepsis doubled in the United States between 2000 and 2008,[2] possibly owing to more chronic diseases in our aging population, along with the rise of antibiotic resistance and the increased use of invasive procedures, immunosuppressive drugs, and chemotherapy.

The cost associated with sepsis-related care in the United States is more than $20.3 billion annually.[3]

DEFINITIONS HAVE EVOLVED

In 1991, *sepsis* was first defined as a systemic inflammatory response syndrome (SIRS) due

to a suspected or confirmed infection with 2 or more of the following criteria[4]:

- Temperature below 36°C or above 38°C
- Heart rate greater than 90/minute
- Respiratory rate above 20/minute, or arterial partial pressure of carbon dioxide less than 32 mm Hg
- White blood cell count less than 4×10^9/L or greater than 12×10^9/L, or more than 10% bands.

Severe sepsis was defined as the progression of sepsis to organ dysfunction, tissue hypoperfusion, or hypotension.

Septic shock was described as hypotension and organ dysfunction that persisted despite volume resuscitation, necessitating vasoactive medication, and with 2 or more of the SIRS criteria listed above.

In 2001, definitions were updated with clinical and laboratory variables.[5]

In 2004, the Surviving Sepsis Campaign guidelines adopted those definitions, which led to the development of a protocol-driven model for sepsis care used worldwide.[6] The US Centers for Medicare and Medicaid Services (CMS) followed suit, defining sepsis as the presence of at least 2 SIRS criteria plus infection; severe sepsis as sepsis with organ dysfunction (including serum lactate > 2 mmol/L); and septic shock as fluid-resistant hypotension requiring vasopressors, or a lactate level of at least 4 mmol/L.[7]

Appropriate antimicrobials should be started within an hour of recognizing sepsis

In 2016, the Sepsis-3 committee[8] issued the following new definitions:

- *Sepsis*—A life-threatening condition caused by a dysregulated host response to infection, resulting in organ dysfunction
- *Septic shock*—Circulatory, cellular, and metabolic abnormalities in septic patients, presenting as fluid-refractory hypotension requiring vasopressor therapy with associated tissue hypoperfusion (lactate > 2 mmol/L).

The classification of severe sepsis was eliminated.

Multiple definitions create confusion

Both the CMS and international consensus definitions are currently used in clinical practice, with distinct terminology and different identification criteria, including blood pressure and lactate cutoff points. The CMS definition continues to recommend SIRS for sepsis identification, while Sepsis-3 uses sequential organ failure assessment (SOFA) or the quick version (qSOFA) to define sepsis (described below). This has led to confusion among clinicians and has been a contentious factor in the development of care protocols.

TOOLS FOR IDENTIFYING HIGH RISK: SOFA AND qSOFA

SOFA is cumbersome

SOFA is an objective scoring system to determine major organ dysfunction, based on oxygen levels (partial pressure of oxygen and fraction of inspired oxygen), platelet count, Glasgow Coma Scale score, bilirubin level, creatinine level (or urine output), and mean arterial pressure (or whether vasoactive agents are required). It is routinely used in clinical and research practice to track individual and aggregate organ failure in critically ill patients.[9] But the information needed is burdensome to collect and not usually available at the bedside to help with clinical decision-making.

qSOFA is simpler…

Singer et al[8] compared SOFA and SIRS and identified 3 independent predictors of organ dysfunction associated with poor outcomes in sepsis to create the simplified qSOFA:

- Respiratory rate at least 22 breaths/minute
- Systolic blood pressure 100 mm Hg or lower
- Altered mental status (Glasgow Coma Scale score < 15).

A qSOFA score of 2 or more with a suspected or confirmed infection was proposed as a trigger for aggressive treatment, including frequent monitoring and ICU admission. qSOFA has the advantage of its elements being easy to obtain in clinical practice.

…but has limitations

Although qSOFA identifies severe organ dysfunction and predicts risk of death in sepsis, it needs careful interpretation for defining sepsis. One problem is that it relies on the clinician's ability to identify infection as the cause of organ dysfunction, which may not be apparent early on, making it less sensitive than SIRS for diagnosing early sepsis.[10] Also, preexisting chronic diseases may influence

accurate qSOFA and SOFA measurement.[11] In addition, qSOFA has only been validated outside the ICU, with limited utility in patients already admitted to an ICU.[12]

Studies have suggested that the SIRS criteria be used to detect sepsis, while qSOFA should be used only as a triaging tool.[11,13]

ANTIMICROBIAL THERAPY

Prompt, broad-spectrum antibiotics

Delay in giving appropriate antibiotics is associated with a significant increase in mortality rate.[14–16] Appropriate antimicrobials should be initiated within the first hour of recognizing sepsis, after obtaining relevant samples for culture—provided that doing so does not significantly delay antibiotic administration.[17]

The initial antimicrobial drugs should be broad-spectrum, covering all likely pathogens. Multidrug regimens are favored to ensure sufficient coverage, especially in septic shock. The empiric choice of antimicrobials should consider the site of infection, previous antibiotic use, local pathogen susceptibility patterns, immunosuppression, and risk factors for resistant organisms. Double coverage for gram-negative organisms and for methicillin-resistant *Staphylococcus aureus* (MRSA) should be considered for patients with a high likelihood of infection with such pathogens.[18] Double gram-negative coverage may be appropriate when a high degree of suspicion exists for infection with multi-drug-resistant organisms such as *Pseudomonas* or *Acinetobacter*. If a nosocomial source of infection is suspected to be the cause of sepsis, anti-MRSA agents are recommended.

Appropriate dosing is also important, as efficacy depends on peak blood level of the drug and on how long the blood level remains above the minimum inhibitory concentration for the pathogen. An initial higher loading dose may be the best strategy to achieve the therapeutic blood level, with further dosing based on consultation with an infectious disease physician or pharmacist, as well as therapeutic drug monitoring if needed.[17]

Consider antifungals

The last few decades have seen a 200% rise in the incidence of sepsis due to fungal organisms.[19] Antifungals should be considered for patients at risk, such as those who have had total parenteral nutrition, recent broad-spectrum antibiotic exposure, perforated abdominal viscus, or immunocompromised status, or when clinical suspicion of fungal infection is high.

Risk factors for fungal infection in septic shock should trigger the addition of echinocandins or liposomal amphotericin B. Azoles are considered appropriate for hemodynamically stable patients.[20]

De-escalation and early cessation

Antibiotics are not harmless: prolonged use of broad-spectrum antibiotics is associated with antimicrobial resistance, *Clostridium difficile* infection, and even death.[21]

A robust de-escalation strategy is needed to balance an initial broad-spectrum approach. A pragmatic strategy may involve starting with broad-spectrum antimicrobials, particularly in the setting of hypotension, and then rapidly de-escalating to an antimicrobial with the narrowest spectrum based on local sensitivity patterns. If the clinical course suggests the illness is not actually due to infection, the antibiotics should be stopped immediately. A rapid nasal polymerase chain reaction test for MRSA to guide de-escalation has been shown to be safe and to significantly reduce empiric use of vancomycin and linezolid.[22,23]

A robust antimicrobial de-escalation strategy needs to balance an initial broad-spectrum approach

Antibiotic de-escalation should be discussed daily and should be an essential component of daily rounds.[17] A 7- to 10-day course or even shorter may be appropriate for most infections,[24,25] although a longer course may be needed if source control cannot be achieved, in immunocompromised hosts, and in *S aureus* bacteremia, endocarditis, or fungal infections.

FLUID RESUSCITATION

Sepsis is associated with vasodilation, capillary leak, and decreased effective circulating blood volume, reducing venous return. These hemodynamic effects lead to impaired tissue perfusion and organ dysfunction. The goals of resuscitation in sepsis and septic shock are to restore intravascular volume, increase oxygen delivery to tissues, and reverse organ dysfunction.

A crystalloid bolus of 30 mL/kg is recommended within 3 hours of detecting severe sepsis or septic shock.[17] However, only limited

data support the benefits of this recommendation, and evidence of harm from sustained positive fluid balance is growing.

Some have cautioned against giving too much fluid, especially in patients who have limited cardiorespiratory reserve.[26] Overzealous fluid administration can result in pulmonary edema, hypoxemic respiratory failure, organ edema, intra-abdominal hypertension, prolonged ICU stay and time on mechanical ventilation, and even increased risk of death.[26,27]

With this in mind, fluid resuscitation should be managed as follows during consecutive phases[28]:

- **Rescue:** During the initial minutes to hours, fluid boluses (a 1- to 2-L fluid bolus of crystalloid solution) are required to reverse hypoperfusion and shock
- **Optimization:** During the second phase, the benefits of giving additional fluid to improve cardiac output and tissue perfusion should be weighed against potential harms[27]
- **Stabilization:** During the third phase, usually 24 to 48 hours after the onset of septic shock, an attempt should be made to achieve a net-neutral or a slightly negative fluid balance
- **De-escalation:** The fourth phase, marked by shock resolution and organ recovery, should trigger aggressive fluid removal strategies.[27]

Antibiotic de-escalation should be discussed daily

Assess volume with dynamic measures

Clinicians should move away from using static measures to assess volume status. Central venous pressure, the static measure most often used to guide resuscitation, has been found to be accurate in only half of cases, compared with thermodilution using pulmonary artery catheters to assess change in cardiac output with volume administration.[29] A 2017 meta-analysis[30] showed that the use of dynamic assessment in goal-directed therapy is associated with lower mortality risk, shorter ICU stay, and shorter duration of mechanical ventilation.

Dynamic measures are used to estimate the effects of additional volume on cardiac output. Two methods are used: either giving a fluid bolus or passively raising the legs. The latter method returns 200 to 300 mL of blood from the lower extremities to the central circulation and is performed by starting the patient in a semirecumbent position, then lowering the trunk while passively raising the legs.

With either method, the change in cardiac output is measured either directly (eg, with thermodilution, echocardiography, or pulse contour analysis) or using surrogates (eg, pulse pressure variation).

Alternatively, changes in cardiac output can be evaluated by heart-lung interactions in a patient on a mechanical ventilator. Changes in intrathoracic pressure are assessed during the inspiratory and expiratory cycle to detect changes in cardiac output using pulse pressure variation, stroke volume variation, and variation in inferior vena cava size.

The dynamic measures mentioned above are more accurate than static measurements in predicting preload responsiveness, so they are recommended to guide fluid management.[31,32] But they do have limitations.[33] Although giving a fluid bolus remains the gold standard for critically ill patients, indiscriminate fluid administration carries the risk of fluid overload. Heart-lung interactions are imprecise for patients with arrhythmias, those who are spontaneously breathing with active effort on the ventilator, and those with an open chest or abdomen. Thus, their use is limited in most critically ill patients.[34]

Unlike other dynamic tests, the passive leg-raise test is accurate in spontaneously breathing patients, for patients with cardiac arrhythmias, and for those on low tidal volume ventilation.[35] Due to its excellent sensitivity and specificity, the passive leg-raise test is recommended to determine fluid responsiveness.[17,32]

Lactate level as a resuscitation guide

Lactate-guided resuscitation can significantly lessen the high mortality rate associated with elevated lactate levels (> 4 mmol/L).[36,37] A rise in lactate during sepsis can be due to tissue hypoxia, accelerated glycolysis from a hyperadrenergic state, medications (epinephrine, beta-2 agonists), or liver failure. Measuring the lactate level is an objective way to assess response to resuscitation, better than other clinical markers, and it continues to be an integral part of sepsis definitions and the Sur-

viving Sepsis Campaign care bundle.[7,8,17] Even though lactate is not a direct surrogate of tissue hypoperfusion, it is a mainstay for assessing end-organ hypoperfusion.

Central venous oxygen saturation-guided resuscitation (requiring central vascular access) does not offer any advantage over lactate-guided resuscitation.[38] Microvascular assessment devices are promising tools to guide resuscitation, but their use is still limited to clinical research.

Although optimal resuscitation end points are not known, key variables to guide resuscitation include a composite of physical examination findings plus peripheral perfusion, lactate clearance, and dynamic preload responsiveness.[17,39]

Balanced crystalloids are preferred over isotonic solutions

Crystalloid solutions (isotonic saline or balanced crystalloids) are recommended for volume resuscitation in sepsis and septic shock. The best one to use is still debated, but over the last decade, balanced solutions have come to be favored for critically ill patients. Growing evidence indicates that balanced crystalloids (lactated Ringer solution, Plasma-Lyte) are associated with a lower incidence of renal injury, less need for renal replacement therapy, and lower mortality in critically ill patients. Moreover, isotonic saline is associated with hyperchloremia and metabolic acidosis, and it can reduce renal cortical blood flow.[40–42]

No proven benefit from colloids

The rationale for using colloids is to increase intravascular oncotic pressure, reducing capillary leak and consequently reducing the amount of fluid required for resuscitation. But in vivo studies have failed to demonstrate this benefit.

One can consider using albumin in sepsis if a significant amount of resuscitative fluid is required to restore intravascular volume.[17] But comparisons of crystalloids and albumin, either for resuscitation or as a means to increase serum albumin in critically ill patients, have found no benefit in terms of morbidity or mortality.[43–45] When considering albumin to treat sepsis or septic shock, clinicians should remember its lack of benefit and its substantial cost—20 to 100 times as much as crystalloids, with an additional cost greater than $30,000 per case with use of albumin.[46]

Hydroxyethyl starch, another colloid, was associated with a higher mortality rate and a higher incidence of renal failure in septic patients and should not be used for resuscitation (**Table 1**).[47]

TABLE 1

Randomized controlled trials of volume replacement in sepsis and septic shock

Author and year	Number of patients	Major findings
Finfer et al,[43] 2004	6,997	No reduction in mortality with albumin compared with saline
Perner et al,[47] 2012	804	Higher risk of death and renal replacement therapy with hydroxyethyl starch compared with Ringer solution
Annane et al,[45] 2013	2,587	No reduction in mortality, need for renal replacement therapy, duration of resuscitation, or length of stay with colloids compared with crystalloids
Caironi et al,[44] 2014	1,818	No reduction in mortality, need for renal replacement therapy, or length of stay with albumin replacement
Young et al,[41] 2015	2,278	No difference in incidence of acute kidney injury, need for renal replacement therapy, or length of stay with balanced solution compared with saline
Semler et al,[40] 2018	15,802	Lower rates of mortality and need for renal replacement therapy with balanced solutions compared with saline

EARLY SOURCE CONTROL

Source control is imperative in managing sepsis and septic shock. Inadequate source control may lead to worsening organ function and hemodynamic instability despite appropriate resuscitative measures.[17] A thorough examination and appropriate imaging studies should be performed to determine the optimal way to control the source and assess the risks associ-

ated with each intervention. If appropriate, source control should be achieved within 6 to 12 hours of diagnosis, once initial resuscitation is completed.[48] The source control can range from removal of infected intravascular devices to a chest tube for empyema to percutaneous or surgical intervention in cases of cholecystitis and pyelonephritis.

RESTORING BLOOD PRESSURE

Persistent hypotension and tissue hypoperfusion after adequate fluid resuscitation are caused by loss of normal sympathetic vascular tone, leading to vasodilation, neurohormonal imbalances, myocardial depression, microcirculatory dysregulation, and mitochondrial dysfunction. Vasopressors and inotropes restore oxygen delivery to tissues by increasing arterial pressure and cardiac output respectively.

Mean arterial pressure is the preferred blood pressure to target during resuscitation. The recommended initial goal is 65 mm Hg. A higher goal of 80 to 85 mm Hg may help patients with chronic hypertension,[49] while a lower target may be better tolerated in patients with reduced systolic function, older patients, and patients with end-stage liver disease.

The passive leg-raise test has excellent sensitivity and specificity for determining fluid responsiveness

These recommendations are based on our understanding of autoregulation of blood flow in the vascular beds of central organs (brain, heart, kidneys). After blood pressure falls below a critical threshold, tissue perfusion decreases linearly. That critical threshold can vary between organ systems and individuals, and the target can later be personalized based on global and regional perfusion as assessed with urine output, mental status, or lactate clearance.[50]

Decisions to titrate vasopressors to achieve mean arterial pressure goals should be balanced against potential adverse effects, including arrhythmias, cardiovascular events, and ischemia.

Norepinephrine is the first-line vasopressor

Few large, multicenter randomized controlled studies have been done to determine the most effective initial and adjunctive vasoactive agents for septic shock. Norepinephrine has shown survival benefit with lower risk of arrhythmia than dopamine.[51–53] On the other hand, 2 systematic reviews found no difference in clinical outcomes and mortality with norepinephrine vs epinephrine, vasopressin, terlipressin, or phenylephrine.[53,54]

Without convincing evidence to support other agents as first-line therapy for septic shock, norepinephrine remains the preferred vasopressor for achieving the target mean arterial pressure and is strongly recommended by the Surviving Sepsis Campaign guidelines, albeit supported by only moderate-quality data.[17,55]

Adding a second vasopressor or inotrope

Another sympathomimetic drug such as vasopressin or epinephrine can be used to either achieve target mean arterial pressures or decrease the norepinephrine requirement. A second vasopressor is routinely added when norepinephrine doses exceed 40 or 50 µg/min.

Vasopressin. Septic shock involves relative vasopressin deficiency. Adding vasopressin as a replacement hormone has been shown to have a sparing effect on norepinephrine, resulting in a lower dose needed. A randomized controlled trial comparing vasopressin plus norepinephrine vs vasopressin monotherapy failed to show any survival benefit or reduction in kidney failure.[56,57] Evidence supporting the use of vasopressin over norepinephrine as a first-line agent remains limited, but vasopressin remains the preferred adjunct with norepinephrine.[56,57]

Epinephrine is recommended by the Surviving Sepsis Campaign guidelines as a second-line vasopressor. It has potent alpha- and beta-adrenergic activity, which increases mean arterial pressure by increasing cardiac output and vasomotor tone. Use of epinephrine is limited by significant risk of tachycardia, arrhythmia, and transient lactic acidosis.[58]

Dopamine use is discouraged in sepsis owing to its propensity to induce tachyarrhythmia and significantly worsen outcomes in this setting.[51,52]

Phenylephrine is a pure alpha-adrenergic agonist that is routinely used in septic shock, albeit with limited data on its efficacy and safety. Vail et al[59] found increased mortality associated with phenylephrine use in septic shock in a multicenter cohort study conducted during a norepinephrine shortage. Phenyl-

ephrine use should be limited to septic shock complicated by significant tachyarrhythmia or as an adjunct for refractory vasodilatory shock until there is more evidence of its benefits.[17]

Angiotensin II was recently approved as a vasopressor for use in septic shock. It activates angiotensin type 1a and 1b receptors to increase intracellular calcium in smooth muscle, promoting vasoconstriction. Clinical data related to its use are limited to a recent trial that showed that the addition of angiotensin II improved blood pressure in patients with refractory vasodilatory shock receiving high-dose vasopressors.[60] The data are still sparse on its safety, and its precise role in refractory shock treatment algorithms has yet to be defined.

Inotropic agents may be required for patients with inadequate cardiac output after fluid resuscitation due to sepsis-induced cardiomyopathy or combined shock. Data are limited suggesting an optimal inotropic agent in septic shock, but epinephrine and dobutamine are most commonly used.[61,62] A comparison of norepinephrine plus dobutamine vs epinephrine in septic shock found no difference in mortality, side effects, or shock duration.[62] Milrinone and levosimendan (not approved in the United States) have been studied, with limited data to support their use over dobutamine.[63,64] The response to use of inotropes should be monitored by measuring changes in cardiac output, central venous oxygen saturation, or other indices of tissue perfusion (**Table 2**).

TABLE 2

Randomized controlled trials of vasopressors and inotropes in septic shock

Author and year	Number of patients	Major findings
Annane et al,[62] 2007	330	No difference in mortality with epinephrine vs norepinephrine ± dobutamine; higher lactate elevation and lower pH in epinephrine group
Russell et al,[57] 2008	780	No reduction in mortality with addition of vasopressin to norepinephrine Survival benefit in patients with septic shock requiring norepinephrine < 15 µg/min Vasopressin had norepinephrine-sparing effect.
De Backer et al,[51] 2010	1,679	Higher rates of mortality and arrhythmia with dopamine than with norepinephrine
Gordon et al,[56] 2016	409	No improvement in kidney failure-free days, use of renal replacement therapy, or mortality with vasopressin
Khanna et al,[60] 2017	344	Angiotensin II increased blood pressure in refractory vasodilatory shock

ROLE OF CORTICOSTEROIDS IS QUESTIONED

Corticosteroids downregulate the maladaptive inflammatory response seen in sepsis and help address relative adrenal insufficiency caused by adrenal suppression or glucocorticoid tissue resistance.[65] In septic shock, they have a vasopressor-sparing role and reduce the duration of shock, ventilator use, and ICU stay.

However, the evidence is not conclusive that giving corticosteroids for sepsis improves clinical outcomes or survival,[66–71] and so they are not recommended in sepsis or severe sepsis if fluid resuscitation and vasopressors are sufficient to restore hemodynamic stability. Rather, they can be added as adjunctive therapy for patients requiring higher doses of vasopressors.[17,65]

Adverse events in studies of corticosteroids were limited to hyperglycemia, hypernatremia, and hypertension, with no increase in superinfections.[71] The limited adverse events, along with a uniform demonstration of shorter shock duration, ventilator duration, and ICU stay, suggest steroids may have a role in managing refractory septic shock.[66–69]

If corticosteroids are used in septic shock, current guidelines recommend hydrocortisone 200 mg per day intravenously as a continuous drip or 50 mg bolus in 4 divided doses for at least 3 days, based on a systematic review showing a longer course of low-dose steroids is associated with a lower mortality rate.[72] There is no clear consensus on whether steroids should be tapered or if abrupt cessation is appropriate, as larger randomized clinical tri-

TABLE 3

Randomized controlled trials of corticosteroids in septic shock

Author and year	Number of patients	Major findings
Annane et al,[68] 2002	300	Lower mortality rate and shorter duration of shock in corticotropin nonresponders with hydrocortisone + fludrocortisone, but not in all patients
Sprung et al,[69] 2008	499	No difference in mortality rate, but shorter duration of shock and no increased risk of superinfection with hydrocortisone
Keh et al,[70] 2016	380	No benefit of hydrocortisone in preventing septic shock or decreasing mortality in severe sepsis
Annane et al,[66] 2018	1,241	Lower mortality rate and shorter duration of shock and mechanical ventilation with addition of hydrocortisone + fludrocortisone.
Venkatesh et al,[67] 2018	3,800	No reduction in mortality with addition of hydrocortisone, but reduced duration of shock, mechanical ventilation and length of stay in intensive care unit

als did not use a tapering strategy and found no difference in shock recurrence.[66,67] In most cases, steroids are stopped after cessation of vasopressors.[65]

Future research should focus on appropriate timing of glucocorticoid initiation after onset of shock and comparing a fixed duration regimen to a clinically guided one.

Etomidate as an induction agent for intubation has been associated with suppression of cortisol synthesis and a reduced response to exogenous steroids. Whether it affects outcomes is unclear. Nonetheless, clinicians should practice extreme caution with etomidate use in septic shock (**Table 3**).[73]

BIOMARKERS

Biomarkers facilitate early diagnosis, identify patients at high risk, and monitor disease progression to guide resuscitation goals and tailor management.

C-reactive protein and erythrocyte sedimentation rate have been used in the past, but with limited success.[74]

Procalcitonin has emerged as a method to help detect bacterial infections early and to guide de-escalation or discontinuation of antibiotics.[75,76] Procalcitonin-guided de-escalation of antibiotics reduces duration of antibiotic exposure, with a trend toward decreased mortality.[77,78]

Galactomannan and beta-D-glucan can be used to detect infections with fungi, specially *Aspergillus*. Beta-D-glucan is more sensitive for invasive *Aspergillus*, while galactomannan is more specific.[79]

Cytokines such as interleukins (eg, IL-6, IL-8, IL-10), tumor necrosis factor alpha, acute-phase proteins, and receptor molecules are currently being studied to determine their utility in sepsis care.

The limited sensitivity and specificity of single biomarkers may be overcome by using a combination of biomarkers, which is a current focus of research.[80] For now, the decision to initiate, escalate, and de-escalate therapy should be based on clinical assessment, with procalcitonin or other biomarkers used as an adjunct to other clinical factors.[17]

USUAL CARE VS PROTOCOLIZED INITIAL RESUSCITATION

In 2001, Rivers et al[61] compared usual care for severe sepsis or septic shock with a protocolized targeting of physiologic end points as goals of resuscitation for the 6 hours before admission to the ICU in a single center. They found a significantly lower mortality rate in the goal-directed therapy group. This finding heavily influenced the bundle-based, goal-directed management strategy recommended by the Surviving Sepsis Campaign in 2004.[81]

However, the protocolized approach has been challenged since then, with 3 large multicenter trials finding that usual care was not inferior to protocolized care in sepsis, with no difference in mortality or length of stay.[82–84] Further, usual care was associated with significantly reduced need for central vascular access, blood transfusions, and dobutamine. A meta-analysis involving nearly 4,000 patients at 138 hospitals in 7 countries found that usu-

al care emphasizing detecting sepsis early and rapidly implementing appropriate antimicrobial therapy and adequate fluid resuscitation was not only equivalent to protocolized care in outcomes but was more cost-effective.[85] (**Table 4**).

Is SEP-1 appropriate?

In January 2013, the State of New York mandated that all state hospitals initiate processes for early detection and treatment of sepsis. In October 2015, the National Quality Forum and CMS implemented these processes nationwide.[7] The resultant CMS SEP-1 quality measure standardizes early management of severe sepsis and septic shock, with the goal of improving outcomes. Its elements are based on the Surviving Sepsis Campaign guidelines and consist of a series of steps that need to be completed within 3 and 6 hours after sepsis is recognized.

Steps to be performed within 3 hours include measuring the serum lactate level, drawing blood cultures, and starting appropriate antibiotics, intravenous fluid resuscitation, and vasopressor support if needed. A lactate level is repeated within 6 hours, and static and dynamic assessment of perfusion must be done to determine the need for additional fluid or vasopressors to improve end-organ perfusion.

SEP-1 overall hospital performance is publicly available on the CMS website (medicare.gov/hospitalcompare/search.html?) and has the potential to be used for financial incentives centered on SEP-1 measure compliance performance.[86]

Although SEP-1 has been adopted as a quality measure, some question its clinical relevance, as many of the core recommendations are not supported by strong evidence.[86,87] Three major trials found that the mortality rate was no lower with bundled sepsis care than with usual care.[82–84] Seymour et al[28] collected New York State Department of Health data for 49,331 patients with sepsis and septic shock and found that more rapid completion of the 3-hour bundle—particularly of antibiotic administration but not of fluids—was associated with decreased hospital mortality. A multicenter retrospective cohort study[88] found that failure to meet SEP-1 criteria for any step other than giving antibiotics did not translate to poor outcomes.

TABLE 4

Randomized controlled trials evaluating early goal-directed care in septic shock

Author and year	Number of patients	Major findings
Rivers et al,[61] 2001	268	Significantly lower mortality rate with protocolized care
Peake et al,[82] 2014	1,600	No reduction in mortality, need for advanced respiratory or renal support, or intensive care unit length of stay with protocolized care
Rowan et al,[85] 2014	1,351	No reduction in mortality, need for advanced respiratory or renal support, or intensive care unit length of stay with protocolized care
Mouncey et al,[83] 2015	1,260	No reduction in mortality, need for advanced respiratory, cardiovascular or renal support, or intensive care unit length of stay with protocolized care

A major concern about mandating SEP-1 is that fluids and broad-spectrum antibiotics will be overprescribed as healthcare systems try to meet CMS-mandated quality measures. Indiscriminate use of these therapies has the potential to cause harm and puts an undue strain on healthcare resources.[89]

The lactate level remains an objective guide to assess response to resuscitation

A call to refine guidance

Sepsis is a multifaceted disease, and its management is complex. Simplified guidelines and quality measures based on sound evidence are needed. Electronic medical record systems show promise for assisting with early and accurate detection of sepsis and have the potential to play an important role.[90,91] Checklists that allow bedside caregivers to exercise their clinical acumen are another approach. The success of optimal care initiatives requires sustained, collaborative quality improvement across different specialties in medicine, nursing, and hospital administration.[92] ■

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